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EXAMINER	
POPA, ILEANA	

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1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,321	KALLIES ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8,9,13-16,19,20,22-25,30-34,37-39 and 41-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8,9,13-16,19,20,22-25,30-34,37-39 and 41-55* is/are rejected.

7)☒ Claim(s) *16 and 33* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 6, 7, 10-12, 17, 18, 21, 26-29, 35, 36, and 40 have been cancelled. Claims 1-5, 8, 9, 13, 14, 16, 19, 20, 30, 31, 38, 39, and 41 have been amended. Claims 48-55 are new.

Claims 1-5, 8, 9, 13-16, 19, 20, 22-25, 30-34, 37-39, and 41-55 are pending and under examination.

2. All rejections pertaining to claims 10-12, 17, 18, 21, 26, 27, and 40 are moot because the applicant cancelled the claims in the reply filed on 06/18/2010.

Claim Objections

3. Claim 16 is objected to because of the following informalities: the claim recites that "the T-cells are selected from CD4+ or CD8+ T-cells". Appropriate correction to "the T-cells are selected from CD4+ and CD8+ T-cells" is required.

4. Claim 33 is objected to because of the following informalities: the claim recites "The cell or non-human organism of claim 31". Claim 31 is drawn to a method. However, it is clear that this is a typographical error. Appropriate correction to "The method of claim 31" is required.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-5, 8, 9, 13-16, 19, 20, 22-25, 30-34, 37-39, and 41-47 remain and the new claims 48-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Glimcher et al. (PGPUB 2002/0059652), in view of each Shaffer et al. (Immunity, 2002, 17: 51-62), Pol et al. (Journal of Biomolecular Screening, 2002, 7: 325-332), and Mountford et al. (Proc. Natl. Acad. Sci. USA, 1994, 91: 4303-4307).

Glimcher et al. teach a method of *in vitro* or *in vivo* screening for agonists or antagonists of terminal differentiation of B- or T-cells, wherein the method could be performed with on XBP-1-deficient mouse cells, embryos or mice and wherein the method comprises contacting XBP-1-deficient B- or T-cells, embryos or transgenic mice with a test compound; the B- or T-cells are ASC or $CD4^+$cells (claims 1, 8, 9, 13-16, 30, 37, 38, 39, 41- 43, 48, 50, 51, 54, and 55) (Abstract; p. 1, paragraphs 0004, 0006, 0008, 0019, 0021, 0031, 0042, 0053; 0081-0083).

Glimcher et al. do not teach screening for compounds capable of modulating Blimp-1 activity (claims 1, 30, and 50). However, they do teach that the XBP-1 transcription factor acts downstream of Blimp-1 (paragraphs 0214 and 0215). Additionally, Shaffer et al. teach that Blimp-1 is the master regulator of plasma cells terminal differentiation, wherein Blimp acts by allowing the expression of specific

transcription factors such as XBP-1 (Abstract, p. 56, Fig. 3, p. 59, Fig. 7, p. 60, column 1, last paragraph, column 2). Based on these teachings, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Glimcher et al. by substituting their XBP-1 with Blimp-1 to achieve the predictable result of screening for agonists or antagonists of terminal differentiation of B- or T-cells.

Glimcher et al. and Shaffer et al. do not teach inserting a nucleic acid encoding a reporter molecule into an intron of the *blimp* locus to obtain a modified *blimp* allele comprising the Blimp coding sequences and the reporter under the control of the endogenous *blimp* regulatory elements (claims 1-3, 30-32, and 50-53). However, doing such was suggested by the prior art. For example, Pol et al. teach that high-throughput screening methods require readouts other than determining the level or activity of the gene of interest. Pol et al. suggest using homologous recombination to place a reporter such as GFP under the control of the endogenous regulatory elements of the gene of interest, wherein the detection of the reporter indicates a cellular phenotype (claims 17 and 19) (Abstract; p. 325, column 1; p. 326, column 1; p. 327, column 2, third and fourth full paragraphs; p. 331, paragraph spanning columns 1 and 2). It is noted that, at the time the invention was made, homologous recombination to obtain cells comprising homozygous or heterozygous modifications was routine in the prior art. For example, Mountford et al. teach using homologous recombination in ES cells to place reporters under the control of regulatory sequences of endogenous genes of interest with or without modifying the endogenous gene, wherein insertion could be within an exon or within an intron (claims 3, 18, and 32) (Abstract, p. 4303, column 2 and Fig. 1). Based

on these teachings, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Glimcher et al. and Shaffer et al. by using homologous recombination to place GFP into an intron of the *blimp* allele to achieve the predictable result of obtaining a genetically modified cell suitable for high-throughput screening of test agents capable of modulating Blimp-1 activity. It is noted that by going so, one of skill in the art would have used a targeting vector as recited in claims 44-47. Additionally, by practicing the screening method according to the combined teachings of Glimcher et al., Shaffer et al., Pol et al., and Mountford et al., one of skill in the art would also have practiced a method of monitoring a B or T-cell, wherein detection of the reporter indicates the commitment of the B or T-cell to terminally differentiate (claims 20 and 22-25).

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

The applicant argues that one of skill in the art would not have been motivated to make a XBP-1 transgenic animal in order to specifically isolate ASC and even if one would attempt, a reporter system based on XBGP-1 would not work uniquely to identify ASCs because XBP-1 is ubiquitously expressed, making XBP-1 practically useless as a plasma cell-specific reporter (see the Nutt Declaration submitted with, Glimcher, paragraph [0003],Reimold et al. (Nature, 2001, 412:300-307), the review paper from the Glimcher group, Iwakoshi et al. (Immunol. Rev., 2003, 194: 29-38). One of skill in the art would conclude that even if one were to attempt, an XBP- 1 based reporter

system would not work to uniquely identify ASCs because of the ubiquitous expression pattern of XBP-1.

This is not found persuasive because the primary reference already teaches XBP-1 transgenic mice, wherein the XBP-1 transgenic mice are used to identify agonists or antagonists of ASCs differentiation.

The applicant argues that, in a more recent reference from the Glimcher group, Iwakoshi et al. (JEM, 2007, 204: 2267-2275) reported high XBP-1 expression in dendritic cells (DCs). These DCs are abundant in the spleen which is also a source for ASCs. Thus, one would expect to "see" a mixture of at least ASCs and DCs, in addition to other cells types in light of the ubiquitous expression pattern of XBP-1. Therefore, the results achieved by the present invention, i.e., identification of ASCs, a rare cell population, are totally unexpected. Applicants have demonstrated that in a Blimpl-GFP transgenic mouse, there was a population of cells which exhibited fluorescence to a uniquely high level in the spleen and in the bone marrow, nearly all of which were ASCs. Further, nearly all ASCs were shown to exhibit fluorescence. Thus, using this unique, high level expression of Blimp-controlled reporter approach, all the ASCs were easily identified and isolated.

The argument of unexpected results in isolating ASCs by using the transgenic animal are not found persuasive. Specifically, claims 1-5, 8, 9, 48, and 49 are not drawn to a composition and not to a method of isolating ASCs by using the composition; at the time the invention was made, obtaining this composition was obvious for the

reasons set forth above. None of the remaining claims requires using a transgenic animal to identify and isolate ASCs. Specifically, the remaining claims encompass an *in vitro* genetically-modified cell (claims 13-19 and 50-55), an *in vitro* method of identifying ASCs by providing a genetically modified hematopoietic cell (claims 20 and 22-25), an *in vitro* method of screening for agonists and antagonists of terminal differentiation of hematopoietic cells by using a genetically modified cell (claims 30-34, 37-39 and 41-43), and a vector (claims 44-47). Since none of the claims are drawn to a method of isolating ASCs by using a transgenic animal, the arguments of unexpected results are not material to the instant claims and rejection.

New Rejections

Claim Rejections - 35 USC § 101

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 50-55, 13, 14, and 16 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Specifically, as written, the claims encompass cells existent in a human being and human beings are non-statutory subject matter.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/
Primary Examiner, Art Unit 1633